PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 February 2001 (12.02.01)	
International application No. PCT/GB00/02516	**Applicant's or agent's file reference** PG3733
International filing date (day/month/year) 30 June 2000 (30.06.00)	**Priority date** (day/month/year) 01 July 1999 (01.07.99)
Applicant BURBIDGE, Stephen, Anthony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 December 2000 (12.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PA ENT COOPERATION TREA T

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

LANE, Graham
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

Date of mailing (day/month/year)
03 juillet 2001 (03.07.01)

Applicant's or agent's file reference
PG3733

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02516

International filing date (day/month/year)
30 juin 2000 (30.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

LANE, Graham
Glaxo Wellcome PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: 020 8966 8000
Facsimile No.: 020 8966 8838
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

LANE, Graham
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: 020 8966 8412
Facsimile No.: 020 8966 8838
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Anman QIU
Telephone No.: (41-22) 338.83.38

Printed: 10-12-2001

PATENT COOPERATION TREATY

IPEA/416

00940669-GB000251 6

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LANE, Graham
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Middlesex TW8 9EP
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05.11.2001
Applicant's or agent's file reference: PG3415/WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02516	30/06/2000	01/07/1999

Applicant
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ferro Vasconcelos, M Tel.+49 89 2399-7905

Form PCT/IPEA/416 (July 1992)

05-11-2001

Express Mail No:
EL395889790US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG3415/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02516	30/06/2000	01/07/1999
International Patent Classification (IPC) or national classification and IPC		
A61K31/00		
Applicant		
GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/12/2000	05.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bochelen, D Telephone No. +49 89 2399 8150

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02516

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-11 as originally filed

Claims, No.:

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02516

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-5, 7 (partially); 3-4, 7-8 with regard to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 3-4, 7-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-5, 7 (partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02516

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 8
	No:	Claims	1-4, 5, 7
Inventive step (IS)	Yes:	Claims	6, 8
	No:	Claims	1-4, 5, 7
Industrial applicability (IA)	Yes:	Claims	1-2, 5-6
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB00/02516

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The applicant is informed that no International Preliminary Report will be carried out in respect of subject-matter which is not covered by the search report, i.e. parts of **claims 1-5 and 7** (Rule 66(1)(e) PCT).

2. **Claims 3-4 and 7-8** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

3. The International Examining Authority agrees with the objection of lack of unity raised by the International Searching Authority. The different inventions are the following:

1. Claims 1, 2 (partially), 3, 4 (partially), 5 (partially), 7 (partially): use of KCNQ2/3 channel openers for treating epilepsy and as muscle relaxant

2. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating fever

3. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating migraine

4. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating depression and bipolar disorders

5. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating bowel disorders

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB00/02516

6. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating dependence

7. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating cancer

8. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating inflammatory processes

9. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating ophtalmic diseases

10. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, as analgesics

11. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating tinnitus

12. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, as anxiolytics

13. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating neurotransmission and CNS disorders

14. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating neurodegenerative disorders and neuroprotection

15. Claims 2, 4-8 (all partially): use of KCNQ2/3 channel openers, as far as not comprised in the previous inventions, for treating cognitive disorders

Since fees for the search of an additional invention, i.e the treatment of migraine with KCNQ2/3 channel openers, were paid this International Preliminary Report relates to inventions 1 and 2.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB00/02516

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 31232 A (ZENECA LTD) 24 June 1999 (1999-06-24)

D2: RUNDFELDT C.: 'Characterization of the K+ channel opening effect of the anticonvulsant retigabine in PC12 cells.' EPILEPSY RESEARCH, (1999) 35/2 (99-107)., XP000972218

D3: TINEL NORBERT ET AL: 'The KCNQ2 potassium channel: Splice variants, functional and developmental expression. Brain localization and comparison with KCNQ3.' FEBS LETTERS, vol. 438, no. 3, 6 November 1998 (1998-11-06), pages 171-176, XP001012549 ISSN: 0014-5793

D4: DOST R. ET AL: 'The anticonvulsant retigabine potently suppresses epileptiform discharges in the low Ca++ and low Mg++ model in the hippocampal slice preparation.' EPILEPSY RESEARCH, (1999) 38/1 (53-66)., XP001012551

D5: KAPETANOVIC I.M. ET AL: 'D - 23129: A new anticonvulsant compound.' CNS DRUG REVIEWS, (1996) 2/3 (308-321)., XP001014121

D6: RUNDFELDT C (REPRINT) ET AL: 'The anticonvulsant drug retigabine is effective on 4-aminopyridine induced epileptiform activity in vitro' EUROPEAN JOURNAL OF NEUROSCIENCE, (AUG 1998) VOL. 10, SUPP. [10], PP. 2028-2028. PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0953-816X., XP001014127 ARZNEIMITTELWERK DRESDEN, DEPT PHARMACOL 1, CORP R&D ASTA MED GRP, D-0144 RADEBEUL, GERMANY;CHARITE BERLIN, DEPT NEUROPHYSIOL, D-10117 BERLIN, GERMANY

D7: TOBER C. ET AL: 'D - 23129.' DRUGS OF THE FUTURE, (1995) 20/11 (1112-1115)., XP001014125

D8: WO 99 21875 A (UNIV UTAH RES FOUND) 6 May 1999 (1999-05-06)

D9: US-A-5 384 330 (DIETER HANS-REINHOLD ET AL) 24 January 1995 (1995-01-24)

D10: BIALER M. ET AL: 'Progress report on new antiepileptic drugs: A summary

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

of the Third Eilat Conference.' EPILEPSY RESEARCH, (1996) 25/3 (299-319). XP002107785

4. **Novelty and Inventive step (Art. 33 (1)(2) and (3) PCT):**

4.1 Document D3 discloses that mutations of KCNQ2 and KCNQ3 genes are associated with epilepsy (D3: p175 col1 §5-col2 §2). Document D8 discloses that modulators of KCNQ2 and KCNQ3 K^+ channel activity are useful for the treatment of epilepsy (D8: p40 l29-p41 l10). These documents do not disclose a KCNQ2/3 channel opener and are thus not relevant for the novelty of the present application.

4.2 The documents D2, D4, D5, D6, D7, D9, D10 disclose that regitabine is a K^+ channel opener and the use thereof for the treatment of epilepsy (D2: abstract, p103 col2 §2-p104 col1 §1; D4: abstract, p57 col1; D5: p311 §2-4, p317 §2; D6: abstract; D7: p1112-1114; D9: col10 example 1 claim 3; D10: p304 col1 §3-p305 col1 §2) and as muscle relaxant (D9: col10 example 1, claim 3). These documents do not disclose that regitabine is an agonist of the KCNQ2/3 K^+ channel subtype.

Invention 1

4.3 Document D1 discloses that KCNQ2 K^+ channel agonists, i.e. openers, are useful for the treatment of epilepsy (D1: p23 §1-2, p27 l13, p28 l1). It is thus considered that the subject-matter of **claims 1-4, 5 and 7** is not new.

Invention 2

4.4 The subject-matter of **claims 2 and 4** is anticipated by document D1 which discloses KCNQ2 K^+ channel agonists for the treatment of migraine (D1: p23 §1-2, p27 l13, p28 l1).

4.5 The prior art neither discloses nor suggests the use of regitabine for the treatment of migraine. It is thus considered that the subject-matter of **claims 6 and 8** is new and involves an inventive step.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB00/02516

5. **Industrial applicability (Art. 33 (1) and (4) PCT):**

For the assessment of the present **claims 3-4, 7-8** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

6. The subject-matter of **claims 5 and 7** is not clear. The diseases which are meant to be treated in said claims are not clearly defined by the term "conditions ameliorated by KCNQ2/3 potassiumchannel opening".

PG3733/PCT

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
Glaxo Wellcome plc
Attn. LANE, Graham
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 ONN
UNITED KINGDOM

Applicant's or agent's file reference PG3733	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 00/ 02516	International filing date *(day/month/year)* 30/06/2000
Applicant GLAXO GROUP LIMITED	
	Date of mailing *(day/month/year)* 11/10/2001

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Joannes Vergoosen

Form PCT/ISA/220 (July 1998)

Express Mail No:
EL395889790US

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PG3733		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02516	30/06/2000	01/07/1999
Applicant		
GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

NEW USES POTASSIUM CHANNEL OPENERS, SUCH AS THE TREATMENT OF EPILEPSY

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 00/02516

Box I Observations wher certain claims were found unsearchable (C ntinuati n of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3,4,7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-8

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-4 relate to compounds defined by reference to a desirable characteristic or property, namely the activity as KCNQ2/3 potassium channel opener. Claims 5 and 7 relate to a therapeutic application which is actually not well defined: "conditions ameliorated by KCNQ2/3 potassium channel opening"
The claims cover all compounds and conditions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/conditions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound/condition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search for the first and third inventions has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compound mentioned in claim 5 in relation to the treatment of epilepsy and migraine.

Claims searched completely: 6,8.
Claims searched incompletely: 1-5,7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2(partially),3,5(partially),7 (partially)

   Use of KCNQ2/3 channel openers for treating epilepsy and as muscle relaxants.

2. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in the previous invention, for treating fever.

3. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating migraine.

4. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating depression and bipolar disorders.

5. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating bowel disorders.

6. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating dependence to any agent.

7. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating cancer.

8. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating inflammatory processes.

9. Claims: 2,4-8 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating ophthalmic diseases.

10. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, as analgesics.

11. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating tinnitus.

12. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions as anxiolytics.

13. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating neurotransmission and CNS disorders.

14. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating neurodegenerative disorders and for inducing neuroprotecion.

15. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating cognitive disorders.

INTERNATIONAL SEARCH REPORT

[redacted]ational Application No
[redacted]/GB 00/02516

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/325 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EMBASE, BIOSIS, EPO-Internal, PAJ, WPI Data, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	RUNDFELDT CHRIS ET AL: "The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells tranfected with human KCNQ2/3 subunits." NEUROSCIENCE LETTERS, vol. 282, no. 1-2, 17 March 2000 (2000-03-17), pages 73-76, XP000972246 ISSN: 0304-3940 page 73, column 1, line 1 -column 2, line 19 --- -/--	1,3,5,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2001	11.10.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	STEIN V (REPRINT) ET AL: "Moderate loss of function of cAMP- modulated KCNQ2 KCNQ3 K+ channels is sufficient to cause epilepsy" JOURNAL OF NEUROCHEMISTRY, (JUL 1999) VOL. 73, SUPP. 'S!, PP. S128-S128. PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0022-3042., XP001014124 the whole document	1,3
X	WO 99 31232 A (ZENECA LTD) 24 June 1999 (1999-06-24)	1-4
Y	page 27, line 27 -page 28, line 19 page 29, line 17 - line 28 page 23, line 3 - line 19	5-8
X	RUNDFELDT C.: "Characterization of the K+ channel opening effect of the anticonvulsant retigabine in PC12 cells." EPILEPSY RESEARCH, (1999) 35/2 (99-107)., XP000972218 page 100, paragraph 3 page 104, column 2, paragraph 2	1,3,5,7
X	TINEL NORBERT ET AL: "The KCNQ2 potassium channel: Splice variants, functional and developmental expression. Brain localization and comparison with KCNQ3." FEBS LETTERS, vol. 438, no. 3, 6 November 1998 (1998-11-06), pages 171-176, XP001012549 ISSN: 0014-5793 page 170, column 1, paragraph 1 - paragraph 2 page 175, column 2, paragraph 2 page 104, column 2, paragraph 2	1,3
X	DOST R. ET AL: "The anticonvulsant retigabine potently suppresses epileptiform discharges in the low Ca++ and low Mg++ model in the hippocampal slice preparation." EPILEPSY RESEARCH, (1999) 38/1 (53-66)., XP001012551	1,3,5,7
Y	table 2 page 61, column 1, line 11 - line 18	6,8

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KAPETANOVIC I.M. ET AL: "D - 23129: A new anticonvulsant compound." CNS DRUG REVIEWS, (1996) 2/3 (308-321)., XP001014121	1,3,5,7
Y	page 309, line 1 - line 7 page 316, paragraph 5 -page 317, paragraph 2	6,8
X	RUNDFELDT C (REPRINT) ET AL: "The anticonvulsant drug retigabine is effective on 4-aminopyridine induced epileptiform activity in vitro" EUROPEAN JOURNAL OF NEUROSCIENCE, (AUG 1998) VOL. 10, SUPP. '10!, PP. 2028-2028. PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 ONE, OXON, ENGLAND. ISSN: 0953-816X., XP001014127 ARZNEIMITTELWERK DRESDEN, DEPT PHARMACOL 1, CORP R&D ASTA MED GRP, D-0144 RADEBEUL, GERMANY;CHARITE BERLIN, DEPT NEUROPHYSIOL, D-10117 BERLIN, GERMANY the whole document	5,7
X	TOBER C. ET AL: "D - 23129." DRUGS OF THE FUTURE, (1995) 20/11 (1112-1115)., XP001014125 page 1112, column 2, paragraph 1 - paragraph 5 page 1114, column 1, paragraph 4	5,7
X	WO 99 21875 A (UNIV UTAH RES FOUND) 6 May 1999 (1999-05-06) page 4, line 15 - line 29 page 40, line 29 -page 41, line 10	1,3
X	US 5 384 330 A (DIETER HANS-REINHOLD ET AL) 24 January 1995 (1995-01-24) example 1 column 1, paragraph 2 - paragraph 3 claim 3	5,7
Y	BIALER M. ET AL: "Progress report on new antiepileptic drugs: A summary of the Third Eilat Conference." EPILEPSY RESEARCH, (1996) 25/3 (299-319). XP002107785 page 304, column 2, paragraph 4	5-8

6

INTERNATIONAL SEARCH REPORT

[redacted]tion on patent family members

[redacted]national Application No
[redacted]T/GB 00/02516

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9931232	A	24-06-1999	AU	1569599 A	05-07-1999
			EP	1036175 A1	20-09-2000
			WO	9931232 A1	24-06-1999
WO 9921875	A	06-05-1999	EP	1037900 A1	27-09-2000
			WO	9921875 A1	06-05-1999
US 5384330	A	24-01-1995	DE	4200259 A1	15-07-1993
			AT	134611 T	15-03-1996
			CA	2086654 A1	09-07-1993
			DE	59205496 D1	04-04-1996
			DK	554543 T3	18-03-1996
			EP	0554543 A2	11-08-1993
			ES	2084914 T3	16-05-1996
			GR	3019653 T3	31-07-1996
			JP	3145220 B2	12-03-2001
			JP	5345752 A	27-12-1993
			MX	9300014 A1	01-07-1993
			SG	48046 A1	17-04-1998
			ZA	9300011 A	05-08-1993

PCT REQUEST PG3733

Original (for **SUBMISSION**) - printed on 30.06.2000 03:16:27 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.90 (updated 10.05.2000)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	United Kingdom Patent Office (RO/GB)
0-7	**Applicant's or agent's file reference**	PG3733
I	**Title of invention**	NEW USES FOR POTASSIUM CHANNEL OPENERS
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence Telephone No. Facsimile No.	 applicant only all designated States except US GLAXO GROUP LIMITED Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom GB GB 020 8966 8000 020 8966 8838
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only BURBIDGE, Stephen, Anthony Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom GB GB

Express Mail No:
EL395889790US

PCT REQUEST PG3733

Original (for **SUBMISSION**) - printed on 30.06.2000 03:16:27 PM

III-2	**Applicant and/ r inv nt r**	
III-2-1	This p rson is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	CLARE, Jeffrey, John
III-2-5	Address:	Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom
III-2-6	State of nationality	GB
III-2-7	State of residence	GB
III-3	**Applicant and/or inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	COX, Brian
III-3-5	Address:	Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	DUPERE, Joseph
III-4-5	Address:	3 East Road Whorley End Cranfield, Bedfordshire MK43 0TD United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB
III-5	**Applicant and/or inventor**	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	HAGAN, Russell, Michael
III-5-5	Address:	Glaxo Wellcome Inc Five Moore Drive Research Triangle Park, NC 27709 United States of America
III-5-6	State of nationality	GB
III-5-7	State of residence	US

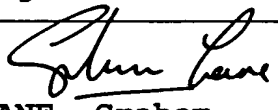
PCT REQUEST PG3733

Original (for **SUBMISSION**) - printed on 30.06.2000 03:16:27 PM

III-6	**Applicant and/or inv nt r**	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	XIE, Xinmin
III-6-5	Address:	2633 Martinez Drive Burlingame, CA 94010 United States of America
III-6-6	State of nationality	~~CN~~ GB
III-6-7	State of residence	US
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	LANE, Graham
IV-1-2	Address:	Glaxo Wellcome plc Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom
IV-1-3	Telephone No.	020 8966 8000
IV-1-4	Facsimile No.	020 8966 8838
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

PCT REQUEST PG3733

Original (for SUBMISSION) - printed on 30.06.2000 03:16:27 PM

V-5	**Precauti nary Designati n Statement** In addition to the d signations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	01 July 1999 (01.07.1999)	
VI-1-2	Number	9915414.8	
VI-1-3	Country	GB	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	11	-
VIII-3	Claims	2	-
VIII-4	Abstract	1	pg3733_abstract.txt
VIII-5	Drawings	0	-
VIII-7	TOTAL	19	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	LANE, Graham	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported internati nal application**	
10-4	**Date of timely receipt of th required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP

PCT REQUEST PG3733

Original (for **SUBMISSION**) - printed on 30.06.2000 03:16:27 PM

10-6	Transmittal of s arch c py delayed until s arch f is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET)

PG3733

Original (for **SUBMISSION**) - printed on 30.06.2000 03:16:27 PM

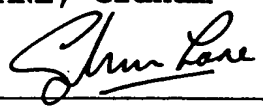
(This sheet is not part of and does not count as a sheet of the international application)

0 0-1	**For receiving Office use only** International Application No.	
0-2	Date stamp of the receiving Office	

0-4 0-4-1	**Form - PCT/RO/101 (Annex)** **PCT Fee Calculation Sheet** Prepared using		PCT-EASY Version 2.90 (updated 10.05.2000)		
0-9	**Applicant's or agent's file reference**		PG3733		
2	**Applicant**		GLAXO GROUP LIMITED, et al.		
12	**Calculation of prescribed fees**		fee amount/multiplier	total amounts (GBP)	
12-1	Transmittal fee	T	⇨	55	
12-2	Search fee	S	⇨	605	
12-3	International fee Basic fee (first 30 sheets)	b1	264		
12-4	Remaining sheets		0		
12-5	Additional amount	(X)	6		
12-6	Total additional amount	b2	0		
12-7	b1 + b2 =	B	264		
12-8	Designation fees Number of designations contained in international application		87		
12-9	Number of designation fees payable (maximum 8)		8		
12-10	Amount of designation fee	(X)	56		
12-11	Total designation fees	D	448		
12-12	PCT-EASY fee reduction	R	-81		
12-13	Total International fee (B+D-R)	I	⇨	631	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**		⇨	1,291	
12-19	**Mode of payment**		authorization to charge deposit account		
12-20	**Deposit account instructions** The receiving Office:		United Kingdom Patent Office (RO/GB)		
12-20-1	is hereby authorized to charge the total fees indicated above to my deposit account		✓		
12-20-2	is hereby authorized to charge any deficiency or credit any over-payment in the total fees indicated above to my deposit account		✓		
12-20-3	is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account		✓		
12-21	Deposit account No.		D01030		
12-22	Date		30 June 2000 (30.06.2000)		

PCT (ANNEX - FEE CALCULATION SHEET) PG3733

Original (for **SUBMISSION**) - printed on 30.06.2000 03:16:27 PM

12-23	Name and signature	LANE, Graham 

VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks Annotate	Please note the abstract may contain Greek characters

13-2-6	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
		Green? Priority 1. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-9	Validation messages Annotate	Yellow! All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/01970 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/GB00/02516

(22) International Filing Date: 30 June 2000 (30.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915414.8 1 July 1999 (01.07.1999) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BURBIDGE, Stephen, Anthony** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **CLARE, Jeffrey, John** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **COX, Brian** [GB/GB]; Glaxo Wellcome PLC, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **DUPERE, Joseph** [GB/GB]; 3 East Road, Whorley End, Cranfield, Bedfordshire MK43 0TD (GB). **HAGAN, Russell, Michael** [GB/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). **XIE, Xinmin** [GB/US]; 2633 Martinez Drive, Burlingame, Ca 94010 (US).

(74) Agent: **LANE, Graham**; Glaxo Wellcome PLC, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/01970 A2

(54) Title: NEW USES FOR POTASSIUM CHANNEL OPENERS

(57) Abstract: The present invention relates to novel uses for retigabine and KCNQ2/3 potassium channel openers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02516

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/325 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EMBASE, BIOSIS, EPO-Internal, PAJ, WPI Data, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	RUNDFELDT CHRIS ET AL: "The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells tranfected with human KCNQ2/3 subunits." NEUROSCIENCE LETTERS, vol. 282, no. 1-2, 17 March 2000 (2000-03-17), pages 73-76, XP000972246 ISSN: 0304-3940 page 73, column 1, line 1 -column 2, line 19 --- -/--	1,3,5,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2001	11.10.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	STEIN V (REPRINT) ET AL: "Moderate loss of function of cAMP- modulated KCNQ2 KCNQ3 K+ channels is sufficient to cause epilepsy" JOURNAL OF NEUROCHEMISTRY, (JUL 1999) VOL. 73, SUPP. 'S!, PP. S128-S128. PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0022-3042., XP001014124 the whole document	1,3
X	WO 99 31232 A (ZENECA LTD) 24 June 1999 (1999-06-24)	1-4
Y	page 27, line 27 -page 28, line 19 page 29, line 17 - line 28 page 23, line 3 - line 19	5-8
X	RUNDFELDT C.: "Characterization of the K+ channel opening effect of the anticonvulsant retigabine in PC12 cells." EPILEPSY RESEARCH, (1999) 35/2 (99-107)., XP000972218 page 100, paragraph 3 page 104, column 2, paragraph 2	1,3,5,7
X	TINEL NORBERT ET AL: "The KCNQ2 potassium channel: Splice variants, functional and developmental expression. Brain localization and comparison with KCNQ3." FEBS LETTERS, vol. 438, no. 3, 6 November 1998 (1998-11-06), pages 171-176, XP001012549 ISSN: 0014-5793 page 170, column 1, paragraph 1 - paragraph 2 page 175, column 2, paragraph 2 page 104, column 2, paragraph 2	1,3
X	DOST R. ET AL: "The anticonvulsant retigabine potently suppresses epileptiform discharges in the low Ca++ and low Mg++ model in the hippocampal slice preparation." EPILEPSY RESEARCH, (1999) 38/1 (53-66)., XP001012551	1,3,5,7
Y	table 2 page 61, column 1, line 11 - line 18	6,8

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KAPETANOVIC I.M. ET AL: "D - 23129: A new anticonvulsant compound." CNS DRUG REVIEWS, (1996) 2/3 (308-321)., XP001014121	1,3,5,7
Y	page 309, line 1 - line 7 page 316, paragraph 5 -page 317, paragraph 2	6,8
X	RUNDFELDT C (REPRINT) ET AL: "The anticonvulsant drug retigabine is effective on 4-aminopyridine induced epileptiform activity in vitro" EUROPEAN JOURNAL OF NEUROSCIENCE, (AUG 1998) VOL. 10, SUPP. '10!, PP. 2028-2028. PUBLISHER: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 ONE, OXON, ENGLAND. ISSN: 0953-816X., XP001014127 ARZNEIMITTELWERK DRESDEN, DEPT PHARMACOL 1, CORP R&D ASTA MED GRP, D-0144 RADEBEUL, GERMANY;CHARITE BERLIN, DEPT NEUROPHYSIOL, D-10117 BERLIN, GERMANY the whole document	5,7
X	TOBER C. ET AL: "D - 23129." DRUGS OF THE FUTURE, (1995) 20/11 (1112-1115)., XP001014125 page 1112, column 2, paragraph 1 - paragraph 5 page 1114, column 1, paragraph 4	5,7
X	WO 99 21875 A (UNIV UTAH RES FOUND) 6 May 1999 (1999-05-06) page 4, line 15 - line 29 page 40, line 29 -page 41, line 10	1,3
X	US 5 384 330 A (DIETER HANS-REINHOLD ET AL) 24 January 1995 (1995-01-24) example 1 column 1, paragraph 2 - paragraph 3 claim 3	5,7
Y	BIALER M. ET AL: "Progress report on new antiepileptic drugs: A summary of the Third Eilat Conference." EPILEPSY RESEARCH, (1996) 25/3 (299-319). XP002107785 page 304, column 2, paragraph 4	5-8

6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/02516

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3,4,7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-8

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2(partially),3,5(partially),7 (partially)

   Use of KCNQ2/3 channel openers for treating epilepsy and as muscle relaxants.

2. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in the previous invention, for treating fever.

3. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating migraine.

4. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating depression and bipolar disorders.

5. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating bowel disorders.

6. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating dependence to any agent.

7. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating cancer.

8. Claims: 2,4-8 (all partially)

   Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating inflammatory processes.

9. Claims: 2,4-8 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, for treating ophthalmic diseases.

10. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers, as far as not comprised in any of the previous inventions, as analgesics.

11. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating tinnitus.

12. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions as anxiolytics.

13. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating neurotransmission and CNS disorders.

14. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating neurodegenerative disorders and for inducing neuroprotecion.

15. Claims: 2,4-8 (all partially)

Use of KCNQ2/3 channel openers as far as not comprised in any of the previous inventions for treating cognitive disorders.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-4 relate to compounds defined by reference to a desirable characteristic or property, namely the activity as KCNQ2/3 potassium channel opener. Claims 5 and 7 relate to a therapeutic application which is actually not well defined: "conditions ameliorated by KCNQ2/3 potassium channel opening"
The claims cover all compounds and conditions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/conditions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound/condition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search for the first and third inventions has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compound mentioned in claim 5 in relation to the treatment of epilepsy and migraine.

Claims searched completely: 6,8.
Claims searched incompletely: 1-5,7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02516

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9931232	A	24-06-1999	AU	1569599 A	05-07-1999
			EP	1036175 A1	20-09-2000
			WO	9931232 A1	24-06-1999
WO 9921875	A	06-05-1999	EP	1037900 A1	27-09-2000
			WO	9921875 A1	06-05-1999
US 5384330	A	24-01-1995	DE	4200259 A1	15-07-1993
			AT	134611 T	15-03-1996
			CA	2086654 A1	09-07-1993
			DE	59205496 D1	04-04-1996
			DK	554543 T3	18-03-1996
			EP	0554543 A2	11-08-1993
			ES	2084914 T3	16-05-1996
			GR	3019653 T3	31-07-1996
			JP	3145220 B2	12-03-2001
			JP	5345752 A	27-12-1993
			MX	9300014 A1	01-07-1993
			SG	48046 A1	17-04-1998
			ZA	9300011 A	05-08-1993